

REMARKS

In the Office Action the Examiner repeated the rejections of claims 45-49 under 35 USC § 103(a) as being unpatentable over **Wassenaar** (U.S. Patent No. 7,060,289) in view of the Merck Manual. The Examiner observes that the Merck Manual teaches that athlete's foot, a fungus infection, commonly grows in warm moist areas between the toes. Further although **Wassenaar** does not teach a method for killing or inhibiting microorganisms including fungi, **Wassenaar** does disclose a single case study of a patient wherein excessive sweating of the forehead and groin resulted in a constant facial rash and chronic fungal infection of his groin. After **Wassenaar** used an anticholinergic amine to reduce the sweating, the facial rash and fungal groin infection improved. Therefore, the Examiner concludes that the combination of the Merck Manual (fungal infections develop in warm moist locations) with **Wassenaar** (excessive sweating may lead to fungal infections and reduction of such sweating causes improvement in the fungal infection) makes it obvious to use anticholinergic amines to inhibit and kill microorganisms including fungi.

Applicant respectfully traverses the Examiner's obviousness finding. The question here turns on what the **Wassenaar** disclosure would have suggested to one of ordinary skill in the art. The experiment reported by **Wassenaar** would demonstrate to one of ordinary skill in the art that reducing the availability of moisture (sweat) can lead to improvement in a facial rash and fungal groin infection. It is not clear from the description in **Wassenaar** that dermatophytic fungus was at all involved in the rash. What is apparent from the reference is that Wassenaar himself believed that the results were entirely due to the reduction of sweating; otherwise there would be no reason to include the addition of antifungal agents (column 7 at line 49). This is the teaching that one of ordinary skill in the art would have perceived. Absent a showing (as in the present application) of actual killing or inhibition of dermatophytic fungi, one of ordinary skill in the art would not interpret **Wassenaar** as showing or suggesting that

glycopyrrolate was effective at killing and inhibition of dermatophytic fungi. Rather the experiment suggests that reducing the level of moisture helps control a fungal groin infection. The question is whether a method of using ACQAs to kill bacteria and dermatophytic fungi would be obvious in light of the **Wassenaar** experiment. At the time of the invention ACQAs were not known to kill or inhibit either bacteria or fungi. It was known that moisture (excess sweat) could favor fungal infections of the skin.

Wassenaar showed that reducing excess sweating by applying glycopyrrolate resulted in apparent improvement of a fungal infection of the skin. Therefore, one of ordinary skill in the art might be motivated to use glycopyrrolate to control fungal infections associated with excess sweating. One of ordinary skill would have not expectation that glycopyrrolate would have any effect on bacteria and fungi except for infection associated with sweating.

The **Wassenaar** experiment does not demonstrate or suggest that ACQAs (such as glycopyrrolate) kill and inhibit microorganisms including dermatophytic fungi. By “killing” one means that the compound has a direct toxic biological effect as opposed to an indirect environmental effect such as by altering the growth environment (i.e., making things drier). Applicant has made the hitherto unknown and unexpected discovery that ACQAs, including glycopyrrolate kill (D-value) and inhibit (MIC) fungi and bacteria in tests. Again the Examiner is directed to paragraphs [0057] to [0063] of the specification. It is known that anti-fungal agents are widely sought; Applicant is the first to recognize the anti-fungal properties of this class of compounds. Applicant also recognizes the association of fungal pathologies with warm and moist environments (see paragraph [0086]) pointed out by the Examiner and exemplified by Experiment 1 of **Wassenaar**. The killing and inhibition of microorganisms, including fungi, by ACQAs above and beyond inhibition due to a moisture reducing effect was not known in the art and is not obvious in face of any of the cited art.

Applicant respectfully points out that it was not obvious and was entirely unexpected to employ ACQAs as agents to kill and inhibit dermatophytic fungi and bacteria. As shown in the Merck reference cited by the Examiner fungal infections (tinea corporis) can occur at any site on the body. Scalp and nail infections are pointed out as being particularly difficult to treat. Therefore, it is apparent that fungal infections are common on areas of the body that are generally not particularly moist. As demonstrated by Applicant's *in vitro* tests, ACQAs do kill and inhibit fungi (*Trichophyton*, a dermatophytic pathogen mentioned in the reference, was used in those tests). The ability of Applicant's inventive method to kill and inhibit dermatophytic fungal pathogens and bacteria on dry parts of the body would not have been obvious in light of any of the cited prior art.

Applicant respectfully suggests that the prior art does not anticipate or render obvious the use of ACQAs to kill and inhibit fungi and bacteria. In the Office Action the Examiner points out that while applicant asserts that the **Wassenaar** experiment does not exhibit killing or inhibition of fungi, the improvement of a fungal infection that was previously resistant to treatment is clearly indicative of at least inhibition of the fungal infection. In response that the infection in question was stated to be chronic—there was no indication that any prior treatment had failed. In this light one of ordinary skill in the art would understand that the improvement in the fungus infection was attributable to the drying (antiperspirant) effect of the treatment. Whereas, the tests reported by Applicant support the effectiveness of ACQA treatments where excessive moisture is not involved. On page 4 of the Office Action the Examiner states that the teaching of **Wassenaar** would make it obvious to one of ordinary skill in the art to employ glycopyrrolate to inhibit growth of microorganisms responsible for fungal infection and malodor. Applicant respectfully points out that **Wassenaar** provides no teaching regarding malodor. **Wassenaar** teaches only reduction in excessive moisture and the possible reduction in a fungus infection which one of ordinary skill in the art would

presume was due to increased dryness. Applicant clearly demonstrates the ability of ACQAs to kill both bacteria and dermatophytic fungi apart from any drying effects of these compounds. The prior art was not aware that ACQAs were effective at both killing and inhibiting dermatophytic fungi and bacteria. Applicant's results show that these agents can work in situations where reduction of excess moisture is not necessarily required. This means that the property of reducing excess sweating may enhance the effectiveness of these agents but is not required for the effectiveness. Faced with the prior art teaching one of ordinary skill in the art would not have expected this.

Applicant directs the Examiner to paragraphs [0055] to [0060]. Paragraph [0058] indicates that ASTM Protocol #1891-97 was used to determine the MIC and D values for ACQAs against common pathological fungi and bacteria that would be found on the skin. One of ordinary skill in the art would immediately understand the impact of the ASTM Protocol studies and their significance. Previously, glycopyrrolate was not known to be a microbial inhibitor or microbicide. The reported tests show that the D value against the dermatophyte *Trichophyton mentagrophytes* was 24 minutes and the MIC activity was in the range of >0.1%. This would cause one of ordinary skill in the art to expect an application of glycopyrrolate to be effective at controlling dermatophytic fungus. Paragraph [0060] reports that other ACQAs show significant activities against a pathogenic yeast (*Candida albicans*) as well as a mold (*Aspergillus niger*).

In view of the foregoing, Applicant respectfully requests the Examiner to withdraw the rejections based on **Wassenaar**. It is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

Amendment to Office Action dated 11 June 2009.
Amendment dated 5 November 2009
Page 8 of 8

Patent Application
Serial No. 10/826,238

If for any reason the Examiner still finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (310) 229-9928 to discuss the steps necessary for placing the application in condition for allowance. You are hereby authorized to charge any fees due and refund any surplus fees to our Deposit Account No. 22-0261. Please reference matter number 94902-256172.

Respectfully submitted,

VENABLE LLP

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